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=> d his

     (FILE 'HOME' ENTERED AT 17:15:13 ON 02 JUN 2008)
     FILE 'REGISTRY' ENTERED AT 17:15:32 ON 02 JUN 2008
          E TENOFOVIR/CN
L1       1 S E3
          SEL L1 NAME
     FILE 'CA' ENTERED AT 17:16:53 ON 02 JUN 2008
L2    1231 S L1 OR E1-6 ("(R)-9-(2-PHOSPHONOMETHOXYPROPYL)ADENINE" OR "GS
           1275"                OR "GS 1278" OR PMPA OR TENEFOVIR OR
           TENOFOVIR)
L3      29 S L2 AND MASS SPECTRO?
L4    3568 S THER!PEUTIC DRUG MONITORING OR TDM
L5     312 S L4 AND(AIDS OR HIV OR ANTIRETROVIRAL OR ANTIVIRAL OR RETROVIRAL
           OR VIRAL)
L6   71523 S (DEPROTE? OR DE PROTE? OR PROTEIN(3A)(REMOV? OR PRECIPITAT?))
L7      18 S L5 AND L6
L8      34 S L5 AND MASS SPECTRO?
L9    1716 S L6 AND MASS SPECTRO?
L10    107 S L9 AND CENTRIFUG?
L11     32 S L10 AND(DRUG OR MEDICINE OR PHARMACEUTICAL)
L12     96 S L3,L7-8,L11
L13     21 S L12 AND PY<2003
     FILE 'BIOSIS' ENTERED AT 17:31:00 ON 02 JUN 2008
L14     31 S L13
     FILE 'MEDLINE' ENTERED AT 17:31:24 ON 02 JUN 2008
L15     19 S L13
     FILE 'CA' ENTERED AT 17:32:00 ON 02 JUN 2008
L16     18 S L10 AND (EVAPORAT? OR RECONSTITUT?)
L17      1 S L16 AND COMPAR?
L18     18 S L16-17
L19      7 S L18 AND PY<2003
     FILE 'BIOSIS' ENTERED AT 17:33:50 ON 02 JUN 2008
L20      3 S L19
     FILE 'MEDLINE' ENTERED AT 17:34:16 ON 02 JUN 2008
L21      4 S L19
     FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 17:35:07 ON 02 JUN 2008
L22     54 DUP REM L13 L19 L14 L20 L15 L21 (31 DUPLICATES REMOVED)

=> d bib,ab,kwic l22 1-54

L22  ANSWER 14 OF 54  CA  COPYRIGHT 2008 ACS on STN
AN   136:47907  CA
TI   LC/MS determination of the intracellular concentration of two novel aryl
     phosphoramidate prodrugs of PMPA and their metabolites in dog PBMC
AU   Lynch, Theresa; Eisenberg, Gene; Kernan, Michael
CS   Gilead Sciences, Foster City, CA, 94404, USA
SO   Nucleosides, Nucleotides & Nucleic Acids (2001), 20(4-7), 1415-1419
AB   LC/MS assays were developed to det. the plasma and intracellular concns.
     of two aryl phosphoramidate prodrugs of the nucleotide analog 9-[2-R-
     (phosphonomethoxy)propyl]adenine.  LC/MS was used to demonstrate the
     presence of high concns. of PMPA in peripheral blood mononucleocytes
     following oral administration of prodrugs in dogs.  High concns. of PMPA
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and active metabolite were detected in MT-2 cells incubated with prodrug using an ion-pairing LC/MS assay.

IT 147127-20-6 (LC/MS detn. of intracellular concn. of two novel aryl phosphoramidate prodrugs of PMPA and metabolites in dog PBMC)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2008 ACS on STN

RN 147127-20-6 REGISTRY

CN Phosphonic acid, P-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy] methyl]- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phosphonic acid, [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy] methyl]- (9CI)

CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, (R)-

OTHER NAMES:

CN (R)-9-(2-Phosphonomethoxypropyl)adenine

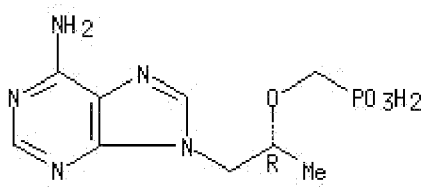
CN GS 1275

CN GS 1278

CN PMPA

CN Tenefovir

CN Tenofovir



L22 ANSWER 16 OF 54 CA COPYRIGHT 2008 ACS on STN

AN 136:318752 CA

TI Antiretrovirals: simultaneous determination of five protease inhibitors and three nonnucleoside transcriptase inhibitors in human plasma by a rapid high-performance liquid chromatography-mass spectrometry assay

AU Villani, Paola; Feroggio, Marina; Gianelli, Luca; Bartoli, Antonella; Montagna, Michela; Maserati, Renato; Regazzi, Mario B.

CS Department of Pharmacology, Universita di Pavia, Pavia, 27100, Italy

SO Therapeutic Drug Monitoring (2001), 23(4), 380-388

AB An anal. technique using liq. chromatog. (LC) coupled with electrospray-mass spectrometry (ESI-MS) has been developed for the simultaneous detn. of five protease inhibitors (PIs): saquinavir, indinavir, ritonavir, nelfinavir, and amprenavir; and three non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine, delavirdine, and efavirenz, in human plasma. This assay allows the elution and identification of these drugs in a single run (10 min) using a linear gradient with water and acetonitrile. The procedure involves liq.-liq. extn. High-performance liq. chromatog. (HPLC) sepn. was achieved on a C18 reversed-phase column, with a linear gradient elution followed by mass spectrometry detection. The calibration curves, obtained by automatic process peak area integration, show a good linearity in a range of concns. between 20 and 10,000 ng/mL (40-10,000 ng/mL for efavirenz). The limit of detection was approx. 10 ng/mL for seven drugs (25 ng/mL for efavirenz). The coeffs. of variation (CV) were always less than 15% for both intra-day and inter-day precision for each compd.

The recovery of the eight drugs ranged from 88.5% to 100%. This novel LC/ESI-MS assay provides an excellent method for simultaneous quant. monitoring of different components of the highly active antiretroviral treatments (HAARTs) in patients treated simultaneously with PIs and NNRTIs, and it has been successfully applied to therapeutic drug monitoring and pharmacokinetic studies.

L22 ANSWER 17 OF 54 CA COPYRIGHT 2008 ACS on STN
AN 136:112099 CA
TI High-performance liquid chromatography of HIV protease inhibitors in human biological matrices
AU Aarnoutse, R. E.; Verweij-van Wissen, C. P. W. G. M.; Underberg, W. J. M.; Kleinnijenhuis, J.; Hekster, Y. A.; Burger, D. M.
CS Department of Clinical Pharmacy, University Medical Center Nijmegen, Nijmegen, 6500 HB, Neth.
SO Journal of Chromatography, B: Biomedical Sciences and Applications (2001), 764(1-2), 363-384
AB Methods for HPLC analysis of protease inhibitors (PIs) in human biological matrices were reviewed. Assays have been developed for analysis of single PIs or for simultaneous measurement of multiple PIs in plasma-serum, saliva, cerebrospinal fluid and semen. Liquid-liquid extraction was most often applied for sample pretreatment, but solid-phase extraction and protein precipitation were used as well. Reversed-phase or ion-pair chromatography have been used to separate PIs. Detection of PIs should be sensitive enough for quantitation of plasma concentrations below trough levels of single PIs, or below proposed therapeutic thresholds for PIs. The large majority of assays employs UV detection. As the potential for interferences is large, the selectivity of every method should be evaluated properly. The available high-performance liquid chromatography (HPLC) methods have been applied in clinical pharmacokinetic studies and for therapeutic drug monitoring of PIs. Participation in an interlaboratory quality control program is recommended for every laboratory engaged in the bioanalysis of PIs.

L22 ANSWER 20 OF 54 BIOSIS on STN
AN 2001:253828 BIOSIS
TI An LC-MS-MS method for the determination of indinavir, an HIV-1 protease inhibitor, in human plasma.
AU Jayewardene, Anura L.; Kearney, Brian; Stone, Judith A.; Gambertoglio, John G.; Aweeka, Francesca T. [Reprint author]
CS Department of Clinical Pharmacy, Drug Research Unit, School of Pharmacy, University of California, San Francisco, CA, 94143-0622, USA aweeka@itsa.ucsf.edu
SO Journal of Pharmaceutical and Biomedical Analysis, (May, 2001) Vol. 25, No. 2, 309-317.
AB A method for the determination of indinavir (IDV) (L-735 524) in human plasma by LC-MS-MS is discussed, and the validation data is presented. The analyte and internal standard are isolated from plasma by a simple acetonitrile precipitation of plasma proteins followed by centrifugation. LC-tandem mass spectrometry in positive ion, multiple reaction monitoring mode used pairs of ions at m/z of 614/421 for indinavir and 628/421 for internal standard, respectively. The calibration curve had a linear range from 3.0 to 12320 ng/ml when linear

least square regression weighing 1/x was applied to the concentration versus peak area plot. The advantages of this method are the fast sample preparation, wide dynamic assay range and quick analysis taking only 5 min for each sample run. The robust nature of this assay has been further verified during routine use over several months involving multiple analysts.

L22 ANSWER 21 OF 54 CA COPYRIGHT 2008 ACS on STN
AN 136:288482 CA
TI Simultaneous simple and fast quantification of three major immunosuppressants by liquid chromatography-tandem mass spectrometry
AU Volosov, Andrew; Napoli, Kimberly L.; Soldin, Steven J.
CS Department of Laboratory Medicine, Children's National Medical Center, Washington, DC, 20010-2970, USA
SO Clinical Biochemistry (2001), 34(4), 285-290
AB The aim of the current study was to develop a simple, fast, and universal method for the quantification of any combination of the 3 major immunosuppressants Sirolimus, tacrolimus, and cyclosporin in whole blood, using a LC-tandem mass spectrometer (API-2000, SCIEX, Toronto, Canada). 250 μL whole blood was spiked with internal std. (Ritonavir), and protein pptd. with 350 μL acetonitrile. The sample was centrifuged and 30 μL aliquot was injected onto the HPLC column, where it underwent an online extn. with ammonium acetate. After that, the automatic switching valve was activated, changing the mobile phase to methanol and thereby eluting the analytes into the tandem mass spectrometer. The high selectivity of a tandem mass analyzer allows detn. of any combination of the 3 drugs within a 5-min run. Between-day precision was between 2.4% and 9.7% for all analytes at the concns. tested. Accuracy ranged between 98.8% and 103.2% (n = 20). The method was linear over the measuring ranges of all analytes. Within-run precision was below %CV = 6% for all analytes. A good correlation with other anal. methods was obsd. The simplicity, universality, and high throughput of the method make it suitable for application in a clin. lab. The method has been implemented in the lab. for a routine use.

L22 ANSWER 22 OF 54 BIOSIS on STN
AN 2002:11054 BIOSIS
TI Separation and identification methods for metalloproteinase inhibitors.
AU Peng, Sean X. [Reprint author]
CS Health Care Research Center, The Procter and Gamble Company, 8700 Mason-Montgomery Road, Mason, OH, 45040, USA peng.sx@pg.com
SO Journal of Chromatography B, (25 November, 2001) Vol. 764, No. 1-2, 59-80.
AB Metalloproteinase inhibitors are being explored for the treatment of a wide variety of human diseases including cancers, arthritis, cardiovascular disorders, human immunodeficiency virus infection, and central nervous system illnesses. This review provides an overview of various analytical sample preparation, separation, detection, and identification techniques employed for the quantitative determination of these inhibitor compounds. Special emphasis is placed on biological sample preparation by automated solid-phase extraction, liquid-liquid

extraction, and protein precipitation by centrifugation or filtration. Other sample preparation methodologies are also evaluated. Applications of high-performance liquid chromatography, gas chromatography, and capillary electrophoresis to the quantitative determination of metalloproteinase inhibitors are described. Examples of qualitative analysis of metalloproteinase inhibitors by hyphenated liquid chromatography with mass spectrometry and nuclear magnetic resonance are also presented. The advantages and limitations of these separation and identification methodologies as well as other less frequently employed techniques are assessed and discussed.

L22 ANSWER 24 OF 54 BIOSIS on STN
AN 2002:499374 BIOSIS
TI Pharmacokinetics of tenofovir disoproxil fumarate in rhesus monkeys.
AU Hamilton, M. [Reprint author]; Gill, S. C. [Reprint author]; Wolf, J. [Reprint author]; Moon-McDermott, L. [Reprint author]
CS Gilead Sciences Inc., Boulder, CO, USA
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 18. Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA. September 22-25, 2001.
AB Background: The antiviral prodrug tenofovir DF (TDF) is being evaluated for treatment of HIV in phase III clinical trials. In preclinical development the pharmacokinetics (PK) of TDF were determined in rhesus monkeys and are here compared to human PK. Methods: Monkeys (3/sex/group) received a single 5.0 or 30 mg/kg intravenous (IV) bolus dose of tenofovir. Fasted monkeys (3/sex) received a single oral 250 mg/kg dose of TDF. One week later, oral TDF was dosed with food at 5.0, 50 or 250 mg/kg to the same groups of monkeys. Plasma samples obtained through 48 hours were assayed for tenofovir using LC/MS/MS (LOQ 1 ng/mL) and the data analyzed by non-compartmental methods. Results: Following an IV 5 or 30 mg/kg tenofovir dose, mean peak plasma concentrations were 13.8+-3.08 and 79.0+-12.6 mg/mL, respectively, and declined biphasically with terminal half-lives (t1/2) of 5.37+-1.35 and 8.79+-2.79 hr. Mean AUC(0-inf) were 5.12+-1.15 and 38.4+-16.2 mgcntdothr/mL. Both Cmax and AUC were dose linear. Oral TDF gave tenofovir plasma mean Tmax values of 0.83-1.1 hr indicating rapid absorption and cleavage of the prodrug. Mean Cmax of 0.113+-0.042, 1.15+-0.676, and 1.68+-1.05 mg/mL were achieved in the 3 dose groups respectively, and declined biphasically with mean t1/2s of 8.23+-1.06, 8.54+-1.14, and 8.41+-1.20 hrs, respectively. Mean AUC(0-inf) were 0.725+-0.125, 6.38+-1.74, and 14.8+-7.81 mgcntdothr/mL. A comparison of Cmax and AUC values suggested dose linear PK between 5 and 50 mg/kg with statistically non-linear PK between the 5 and 250 mg/kg doses. Conclusions: Similar oral bioavailability of TDF was observed between monkeys (32%, 5 mg/kg) and humans (25% fasted, 39% fed, 4 mg/kg) although no food effect was observed in monkeys. Tenofovir clearance was 4-5 fold faster in monkeys for both IV tenofovir and oral TDF compared with humans, with similar volume of distribution, suggesting faster renal clearance in monkeys.

L22 ANSWER 31 OF 54 MEDLINE on STN
AN 2001004291 MEDLINE
TI Therapeutic drug monitoring of antiretroviral agents.

AU Bean P; Patnaik M; Graziano F M; Aziz D C
CS Millennium Strategies, Madison, WI 53717, USA.. PamelaBean@home.com
SO American clinical laboratory, (2000 May) Vol. 19, No. 4, 20-2.
AB HIV+ patients fail antiretroviral therapy due to inadequate drug concentrations reaching the site of viral replication and/or the development of viral resistance to the antiretroviral agents. Adequate drug concentrations may not be reaching the virus due to poor compliance, poor absorption, or other pharmacokinetic factors such as metabolism, elimination, and drug interactions. The most important and most common pharmacokinetic drug interactions involve inhibition of metabolism, induction of metabolism, altered drug absorption, inhibition of renal excretion, and displacement from plasma protein binding sites. If a patient is failing antiretroviral therapy, TDM of antiretroviral agents could help in determining both adequacy of drug concentrations and patients' adherence. Ongoing studies will determine whether total drug concentration or free drug concentration of the protease inhibitors is the best predictor of response. Trough concentrations could prove to be the most important predictor of response, but additional studies are needed to compare trough, peak, and AUC concentrations with response to treatment. Finally, if some patients fail therapy due to inadequate drug concentrations, then increasing the dose could benefit patients' outcome and increase longevity. Clinical trials are needed that compare patients who receive a fixed-dosage regimen with patients who have adjusted dose regimens. Such a study is the best way to determine the true value of TDM of the antiretrovirals.

L22 ANSWER 48 OF 54 MEDLINE on STN
AN 93261007 MEDLINE
TI Measurement of benzoylecgonine in whole blood using the Abbott ADx analyzer.
AU Yee H Y; Nelson J D; Papa V M
CS Detroit Medical Center University Laboratories, MI 48201.
SO Journal of analytical toxicology, (1993 Mar-Apr) Vol. 17, No. 2, 84-6.
AB An alternate procedure has been developed for the processing of whole blood for the estimation of benzoylecgonine with the use of the Abbott ADx reagents and analyzer. This procedure allows for handling of relatively large numbers of samples without the need to evaporate extraction solvent. Blood samples were diluted with an equal volume of phosphate buffer-methanol (80:20 v/v), and the proteins were removed by centrifugation through a membrane filter device. A comparison of the proposed method with an acetone solvent extraction procedure has been made, and results were shown to be equivalent. Recoveries of 94-105% benzoylecgonine were obtained for added concentrations of 25-500 ng/mL.

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STN INTERNATIONAL LOGOFF AT 17:35:50 ON 02 JUN 2008